REMARKS

Claims 1-20 are pending in the instant application. Claims 1-11 have been withdrawn from consideration. Claims 12-20 have been rejected. Claims 1-20 have been canceled. New claims 21 and 22 have been added to incorporate subject matter of the canceled claims. No new matter has been added by these additions to the claims. Reconsideration is respectfully requested in light of these additions and the following remarks.

I. Election/Restriction

The Restriction Requirement placing claims 1-11 into Group I and 12-20 into Group II has been deemed proper and made Final. Accordingly, Applicants have canceled claims 1-11, without prejudice, reserving the right to file continuing applications on the canceled subject matter.

II. Priority

The Examiner suggests that the Applicant's claim of priority is not valid as there was no support for the combination of antisense therapy with another therapy in the cited priority

applications, in particular the use of antisense combined with gemcitabine. Although Applicants do not agree with the Examiner's contention that the application is not entitled to the proposed priority claim, it has been deleted to facilitate prosecution of the application.

III. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 12-20 have been rejected under 35 U.S.C. 102(b) as being anticipated by Calabretta et al. (WO 94/08625). The Examiner suggests that this patent application discloses a method for modulating human ras, including N-ras, H-ras, and K-ras, including combining said antisense with at least one chemotherapeutic agent such as doxorubicin. The Examiner suggests that this reference also teaches use of an amount which kills cancer cells while sparing normal hematopoietic cells, as well as treatment of diseases, including ras-associated diseases, and purging of bone marrow. Applicants respectfully traverse this rejection.

At the outset, Applicants have canceled claims 12-20 and added new claims 21 and 22 which are drawn to subject matter of the canceled claims. Support for these claims can be found throughout the specification as filed.

Calabretta et al. disclose antisense compounds targeted to human ras and their use to treat cancer, as well as combining the antisense compounds with administration of doxorubicin. Nowhere does this patent application teach or suggest combining ras targeted antisense with the specific chemotherapeutic agent as claimed. In order to anticipate an invention the cited reference must teach each and every limitation of the claims (MPEP 2131). This reference fails to teach the presently claimed invention. Therefore, withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 12-20 have been rejected under 35 U.S.C. 103(a) as being anticipated by Calabretta et al., in view of Possinger et al. (1995). The Examiner suggests that it would have been *prima facie* obvious for one of skill in the art to modify the method of Calabretta et al. to use gemcitabine in combination therapy since this reference expressly teaches that the non-antisense component may comprise an anti-neoplastic agent useful in the treatment of the particular diseases. The Examiner suggests that motivation is provided by the teachings as well. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

As discussed *supra*, Calabretta et al. fail to teach the use of gemcitabine in combination with antisense compounds targeted to ras. Although Possinger et al. teach the use of gemcitabine in cancer, nowhere does this combination of references provide one of skill with an expectation that the combined treatment regimen would be successful in treating or preventing cancer, or at inhibiting proliferation of cancer cells. No data are provided in these references showing such *in vivo* activity. It is only with the specification in hand that one of skill would understand that these entities, antisense to ras and gemcitabine, could be used successfully and safely in patients to prevent or treat cancer. Accordingly, the combination of cited prior art fails to provide one of skill with such an expectation of success and fails to

establish a prima facie case of obviousness. Withdrawal of this rejection is therefore respectfully requested.

V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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